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ORIGINAL ARTICLE

A desflurane and fentanyl dosing regimen for wake-up testing during scoliosis surgery: Implications for the time-course of emergence from anesthesia

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Background/Purpose: The Stagnara wake-up test assesses neurological deficits during scoliosis surgery, and response surface interaction models for opioids and inhaled agents predicts anesthetic drug effects. We hypothesized that there is an optimal desflurane–fentanyl dosing regimen that can provide a faster and more predictable wake-up time, while also ensuring adequate analgesia during wake-up testing.
Methods: Twenty-three American Society of Anesthesiologists Class I–II scoliosis patients who received desflurane–fentanyl anesthetic regimens were enrolled in this posthoc study, and their intraoperative drug administration data were collected retrospectively. Desflurane and fentanyl effect site concentrations were calculated using pharmacokinetic models, and converted to equivalent remifentanil–sevoflurane concentrations.
Results: Results were fitted into Greco models for predicting the probability of an Observers Assessment of Alertness/Sedation score of <2. At time of wake-up, the models correctly predicted the probability that patients would respond to voice prompts and prodding was approximately 50%. The probability of pain intensity was distributed between 50% and 95%, indicating a low degree of pain at emergence. When comparing subgroups defined by calculated effect-site fentanyl concentrations, the wake-up time in the intermediate concentration group was significantly shorter than that in the high concentration group ($p = 0.024$).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: This study provides evidence that desflurane—fentanyl-based anesthesia is conducive to rapid emergence followed by an immediate neurological evaluation. Intermediate fentanyl effect-site concentrations (1—2 ng/mL) at time of wake-up were associated with good balance between rapid emergence and adequate analgesia. Furthermore, we believe that generalizing response surface models to a variety of inhalation agent-opioid combinations using simple relative potency relationships is possible and practical.

Introduction

The Stagnara wake-up test has been used to assess neurological deficits during scoliosis surgery since 1973.[1] In this test, the patient is briefly allowed to emerge from anesthesia to participate in a neurological assessment, while still remaining adequately sedated and receiving sufficient analgesia to tolerate pain from the incision and endotracheal tube.[2] Although somatosensory-evoked potentials and motor-evoked potentials have replaced wake-up testing as the standard neurological testing, the wake-up test is still used by many surgeons.[3—8] It can be challenging for the anesthesiologist to achieve both rapid wake-up onset and adequate analgesia during scoliosis surgery. To our knowledge, there is still no practice guideline that informs anesthesiologists of which anesthetic combination is optimal for intraoperative wake-up testing.

Response surface interaction models investigate drug interactions. It can be used to predict clinical outcomes such as loss of response to verbal command, reduced perception, loss of response to noxious stimuli, the occurrence of unwanted side effects, or predicting certain physiology-based monitor values.[3] Response surface interaction models for opioids and inhaled agents have been used to predict anesthetic drug effects such as analgesia, sedation, and loss of responsiveness.[4—6] Potency between different medications can be converted and the converted doses can be compared just like different opioids can be converted into morphine equivalent doses for comparison.[6] We have established a sevoflurane—remifentanil interaction model based on observations in volunteers and found that an Observers Assessment of Alertness/Sedation (OAA/S) score of <2, in which the patient responds only after moderate prodding or shaking, is a good surrogate model for wake-up testing.[7] In our previous work, a sevoflurane—remifentanil interaction model was adapted to test desflurane—fentanyl, and shown to accurately predict patients' responses during wake-up testing. Based on these results, we hypothesized that there is an ideal desflurane—fentanyl regimen that enables a faster wake-up time (<10 minutes), more accurate prediction of waking, and adequate analgesia, thereby allowing patients to complete a neurologic assessment.

The aim of the present study was to identify an optimized desflurane—fentanyl dosing regimen for wake-up testing based on actual dosing regimens, and to model predictions of responsiveness and analgesia.

Materials and methods

Patients

Previously collected data were used in the present study. The parameters analyzed included anesthesia, wake-up procedure, and data derived from the aforementioned pharmacokinetic simulation and response surface models.[7] The Taipei Veterans General Hospital Review Board (Taipei, Taiwan) approved the study. The Institutional Review Board agreed that no written informed consent from the participants was needed while all patient records/information was anonymized and deidentified prior to analysis. Twenty-three American Society of Anesthesiologists (ASA) Class I—II patients that underwent surgical scoliosis correction under general anesthesia with desflurane—fentanyl between 2005 and 2011 were retrospectively enrolled, and their medical charts were reviewed.

Anesthesia

A standardized anesthesia protocol was followed, comprising induction with propofol (2 mg/kg), fentanyl (5 μg/kg), and cisatracurium or rocuronium to facilitate endotracheal intubation. Maintenance was conducted with desflurane and bolus doses of fentanyl to keep blood pressure and heart rate within 20% of baseline, and intermittent bolus injections of cisatracurium were given to maintain one twitch after train-of-four stimuli conditions. The tidal volume was set at 8 mL/kg, and end-tidal carbon dioxide was maintained between 32 mmHg and 36 mmHg by adjusting the tidal volume.

Wake-up testing

The timeline of events are presented in Figure 1. Administration of cisatracurium and fentanyl was interrupted 30 minutes before the anticipated initiation of the wake-up test (T_0). The wake-up test was initiated upon the surgeon's request, and the desflurane vaporizer was turned off (T_1). Fresh gas flow was increased to 4 L/min.

During the wake-up test, patients were addressed loudly by their first name, and asked, "can you move your fingers and toes?" If they did not respond within 2 seconds, the procedure was repeated at 10-second intervals until they did respond. Wake-up time was defined as the duration of time between the desflurane vaporizer being turned off

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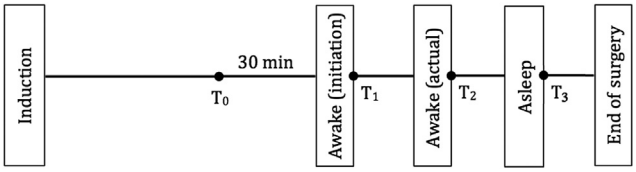

Figure 1 Timeline of events. T_0: 30 minutes before anticipated initiation of wake-up, as set by the surgeon, cisatracurium and fentanyl were discontinued; T_1: initiation of wake-up. Desflurane vaporizer was turned off. T_2: actual time of wake-up. Patients moved their fingers and toes. T_3: resume desflurane and fentanyl, end of wake-up testing.

(T_1) and the first time the patient moved their fingers and toes (T_2). A "moderately painful stimulus" [defined as 30 pounds per square inch (PSI) or 207 pascals of anterior tibial pressure][5,6] was also applied every 15 seconds. After neurological testing, desflurane and fentanyl resumed and that concludes the wake-up testing (T_3). We recorded the time each drug was administered, surgical events, end-tidal desflurane concentrations, and patient responses to surgical stimuli, pain stimuli, and verbal commands.

Modeling of effect-site concentrations

A response surface model of remifentanil and sevoflurane, which was established previously in a volunteer study, was used for comparison.[3,5] The concentrations of fentanyl and desflurane need to be converted to remifentanyl and sevoflurane concentrations to fit this model. We used fentanyl pharmacokinetic models[8,9] to calculate fentanyl effect-site concentrations throughout the procedure, and these values were converted to equivalent remifentanil effect-site concentrations based on a relative potency of remifentanil to fentanyl of 1:1.2.[10–12] A desflurane pharmacokinetic model was used to calculate brain tissue concentrations.[13,14] Desflurane brain tissue concentrations were converted to equivalent sevoflurane effect-site concentrations based on a potency equivalence of sevoflurane to desflurane of 3.3:1. The response surface models for predicting the probability of an OAA/S score of <2,[15] which the patient responds only after moderate prodding or shaking, at given remifentanil and sevoflurane concentrations were established based on data collected from volunteers in previously reported studies.[3,5] Table 1 shows the parameters estimated by the two models, which were based on a Greco model structure.[16]

The probability that the patient would not respond to a 30-PSI anterior tibia stimulus was calculated via a previously established model.[4]

Evaluation of response surface model predictions

Model predictions of the likelihood of an OAA/S score of <2 and no response to 30 PSI of anterior tibial pressure ranging from 0% to 100% were calculated every 10 seconds, beginning with termination of the anesthetic and ending 10 minutes after each patient woke up. Model predictions were compared with clinical observations and graphical analyses.

Table 1 Sevoflurane–remifentanil interaction model.

	OAA/S score < 2	Pressure algometry (30 PSI)
Model parameters		
C_{50} remifentanil (ng/mL)	23.10	1.27
C_{50} sevoflurane (vol%)	0.78	0.83
Interaction (α)	26.68	0.91
Steepness (n)	2.46	2.71

Model parameters were fit to a Greco model structure from responses recorded in volunteers.
C_{50} = effect-site concentrations that produced 50% of the maximal effect when remifentanil or sevoflurane was administered; OAA/S = Observer's Assessment of Alertness/Sedation; PSI = pounds per square inch; α and n = model parameters representing the steepness of the dose-response relationship and the interaction between sevoflurane and remifentanil.[7]

Graphical analysis

Predictions from each model for OAA/S were compared graphically. A plot of the desflurane–fentanyl concentrations at the time of emergence was superimposed onto a topographical representation of the response surface model predictions for an OAA/S score of <2 and no response to 30 PSI of anterior tibial pressure (pressure algometry). The topographical plot included the 5%, 50%, and 95% isoboles. We defined isoboles as the set of desflurane–fentanyl concentration pairs that produced the same probabilities of effect.

The fentanyl effect-site concentrations were calculated for each patient at the beginning of wake-up testing. According to these calculations, we divided the 23 patients into three subgroups: L (low initial fentanyl group, < 1 ng/mL), I (intermediate initial fentanyl group, ≥ 1 ng/mL and < 2 ng/mL), and H (high initial fentanyl group, ≥ 2 ng/mL). The mean durations of the time from the beginning of wake-up testing (T_1) until the observed wake-up time (T_2) in each of the three groups were compared via a nonparametric Kruskal–Wallis test.[17] The Mann–Whitney U test[18] was also employed to analyze the three sample pairs for significant differences. Boxplots and Kaplan–Meier analyses were used to perform graphical comparisons. All plots were constructed using Sigmaplot 12 (Systat Softeware, Inc., San Jose, CA, USA) and Matlab R2013b (The Mathworks Inc., Natick, MA, USA).

Results

Table 2 lists the demographics and surgical times for the 23 patients in the study. Three surgeons and 11 anesthesiologists in total participated in the procedures analyzed in this study. After recovery, none of the patients reported recalling any portion of the procedure except for events that occurred during the wake-up test, and none recalled pain during the test.

The mean duration of time from desflurane being turned off (T_1) to the patient waking up (T_2) was 10.3 ± 4.7 minutes. Figure 2 shows the three new response surface model's predictions of the probabilities that each patient

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Table 2 Patient demographic data and surgery statistics.

Groups	L ($n = 4$)	I ($n = 6$)	H ($n = 13$)	p
Age (y)	14.8 ± 1.5	16.0 ± 3.2	16.2 ± 3.2	0.601
Sex, n (male/female)	1/3	3/3	4/9	0.646
ASA, n (I/II)	2/2	3/3	8/5	0.858
Weight (kg)	52.5 ± 6.0	52.3 ± 8.5	50.5 ± 9.9	0.956
Height (cm)	162.9 ± 6.2	164.6 ± 9.4	160.5 ± 5.2	0.535
BMI (kg/m^2)	19.8 ± 2.5	19.2 ± 1.0	19.7 ± 4.1	0.905
Intubation to T_3 (min)	261.3 ± 44.8	236.0 ± 41.7	275.0 ± 61.2	0.183
T_1 to T_2 (min)	7.1 ± 5.6	7.9 ± 3.7	12.3 ± 4.1	0.046
T_3 to end of anesthesia (min)	157.5 ± 18.5	165.0 ± 34.8	153.3 ± 45.5	0.517

Data are represented as mean $\pm$ standard deviation.
ASA = American Society of Anesthesiologists; BMI = body mass index; H = high initial fentanyl group; I = intermediate initial fentanyl group; Intubation to T_3 = duration of time from endotracheal intubation to end of wake-up testing (T_3); L = low initial fentanyl group; T_1—T_2 = duration of time from desflurane being turned off (T_1) to the patient waking up (T_2); T_3 to end of anesthesia = duration of time from end of wake-up testing (T_3) to end of anesthesia.

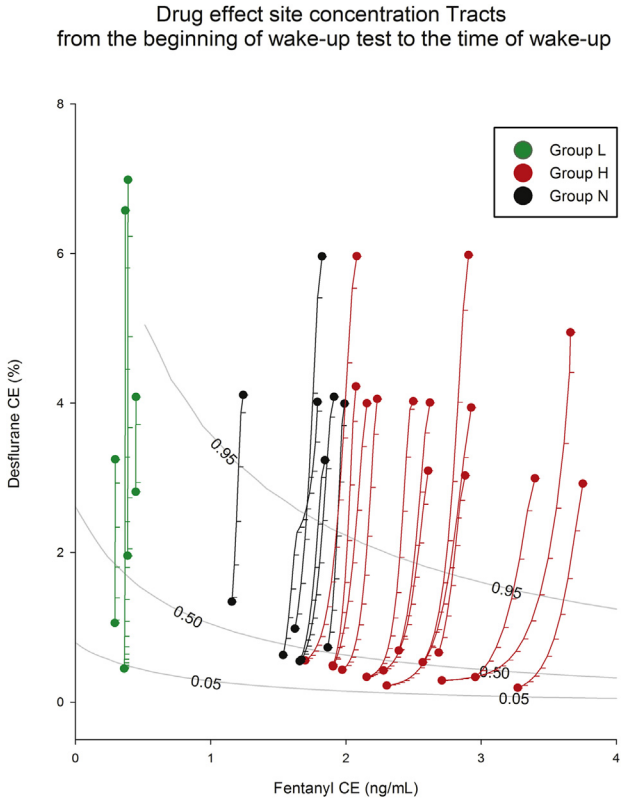

Figure 2 Drug effect-site concentrations from the beginning of wake-up testing to actual emergence. Drug effect-site concentration pairs changing tracks from initiation of wake-up testing (T_1) to actual emergence (T_2) presented as the % volume of the desflurane—fentanyl effect-site concentrations for each of the 23 patients. The concentration pairs are shown with three probabilities from the Observers Assessment of Alertness/Sedation score <2 response surface model. The dash-dot, solid, and dotted lines represent the 95%, 50%, and 5% model-predicted probabilities, respectively. Black, red, and green lines represent the median, high, and low initial fentanyl effect-site group pairs, respectively. All track line ticks represent 1 minute. CE = effect site concentration; Group H = high initial fentanyl group; Group I = intermediate initial fentanyl group; Group L = low initial fentanyl group.

would respond to a loud voice command and moderate prodding 20 minutes before and 10 minutes after the time the patient actually moved their fingers and toes during the wake-up test. At the time the patients responded, the response surface model's prediction of the probability of an OAA/S score of <2 had a mean of 56.2% $\pm$ 26.7%. Figure 2 also shows the reductions in desflurane and fentanyl

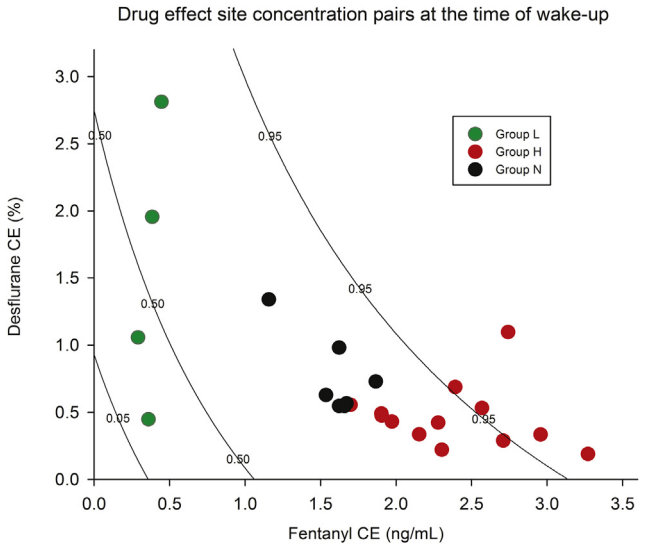

Figure 3 Calculated drug effect-site concentration pairs at the time of wake-up. Drug effect-site concentration pairs at the time of wake-up are presented as volume% for the desflurane and fentanyl effect-site concentrations for each of the 23 patients. The concentration pairs are shown in conjunction with three probabilities from the pressure algometry (probability of no response to 30 PSI of anterior tibial pressure) response surface model previously developed in a laboratory study of volunteers.[4,5] Black dots represent the median initial fentanyl effect-site group pairs, red stars indicate the high initial fentanyl effect-site group pairs, and green dots represent the low initial fentanyl effect-site group pairs. CE = effect site concentration; Group H = high initial fentanyl group; Group I = intermediate initial fentanyl group; Group L = low initial fentanyl group.

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effect-site concentrations during wake-up testing. The three black curves show the concentrations where there were 5%, 50%, and 95% probabilities of an OAA/S score <2. The final concentrations (those predicted for when the patient moved their fingers and toes) were approximately equally distributed, and the probability that patients would respond to voice prompts and prodding were approximately 50%; 16 patients had concentrations >50% and seven had concentrations <50%. Desflurane concentrations fell more rapidly than fentanyl concentrations.

Figure 3 shows the desflurane and fentanyl effect-site concentration pairs for each patient at the time of emergence plotted in conjunction with isoboles of the previously developed response surface model for 30 PSI of anterior tibial pressure. The effect-site concentration pairs for desflurane and fentanyl were mainly distributed between model predictions of 50% and 95%, with only two patients, both in group L, that had concentrations less than 50%.

The patients' mean wake-up durations (from T_1 to T_2) in groups L ($n = 4$), I ($n = 6$), and H ($n = 13$) were 7.13 ± 5.60 minutes, 7.89 ± 3.67 minutes, and 12.30 ± 4.10 minutes, respectively. There was a significant wake-up time difference between the three groups detected with a Kruskal–Wallis test ($p = 0.046$). A Mann–Whitney U test for Group I versus Group H also revealed a significant difference ($p = 0.048$), whereas the other two comparisons (L vs. I and L vs. H) were not statistically significant ($p = 0.522$ and 0.054, respectively). The Kaplan–Meier curves for the three initial fentanyl effect-site concentration groups are shown in Figure 4.

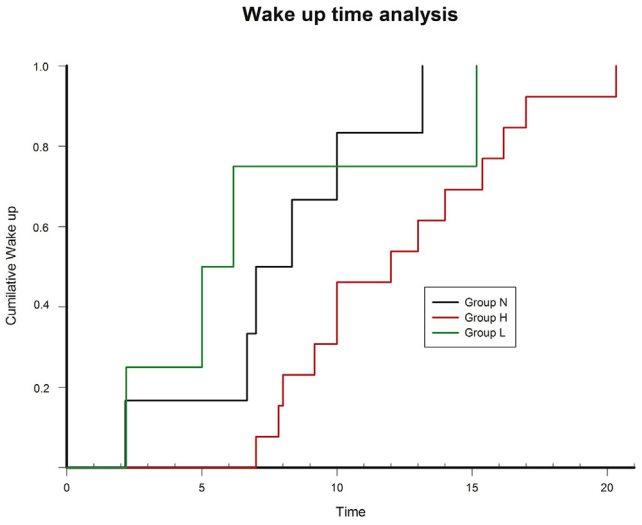

Figure 4 Wake-up time analysis. The Kaplan–Meier curves for the three initial fentanyl effect-site concentration groups. The wake-up time in Group H was significantly longer than that in Group I ($p = 0.024$) but no statistical significance were found between Groups H and L or between I and L. Group H = high initial fentanyl group; Group I = intermediate initial fentanyl group; Group L = low initial fentanyl group.

Discussion

On average, patients moved their fingers and toes within 3 minutes of the 50% model prediction probability for regaining consciousness. Before beginning wake-up testing, the model predicted >95% probabilities of the patient being unconscious, which was consistent with intraoperative observations. Once the anesthetic was terminated at T_1, the model predictions rapidly decreased, and patients emerged from anesthesia over a wide range of model predictions. Although more than 79% of patients woke up within 5 minutes of the 50% model prediction, the overall distribution of the time differences was large (Figure. 2). Notably, among the five longest time differences presented in Figure 3, ranging from 5.5 minutes to 10.3 minutes, three of them were in the low initial fentanyl effect-site concentrations group (Group L), which only contained four patients. The mean initial of fentanyl effect-site concentration in group L was 0.375 ± 0.063 ng/mL, whereas the remaining 19 patients had a mean initial fentanyl concentration of 2.443 ± 0.680 ng/mL. For patients in this group, response surface models used to predict wake-up time may need to be adjusted to improve model predictions.

The model predictions for no response to pain at wake-up time were generally consistent with intraoperative observations (Figure 3). For the majority of patients, the model predicted that the probability of no response to 30 PSI of tibial pressure was >50%. However, the analgesic effects were difficult to evaluate because the patients were intubated, and none of them recalled the wake-up test after they woke up in the postanesthesia care unit. Only two patients in the low initial fentanyl effect-site concentration group (Group L) had model predictions of no response to tibial pressure of <50%. These individuals might have had a high risk of poor analgesia quality, which can cause severe complications such as irritability and falling from the table during spine surgery. Based on the results of the present study, we cannot be sure that a tibial pressure of 30 PSI is an appropriate surrogate indicator of the level of pain during the wake-up period in scoliosis correction surgery. However, the results were difficult to interpret, as we only evaluated a small sample of patients who underwent a range of extents of scoliosis corrective surgery, which are associated with different degrees of pain.

Although the bispectral index score and A-line autoregressive index are widely used in clinical anesthesia, they cannot predict the results of the wake-up test well, especially during opioid-dominant anesthesia.[19,20] Grottke and coworkers[21] concluded that desflurane-based anesthesia was most likely to achieve this predictive goal. Desflurane allowed rapid and predictable awakening during intraoperative wake-up testing.[22]

The longer wake-up time in the high initial fentanyl group in comparison to the normal and low fentanyl groups was most likely due to fentanyl's long half-life. Fentanyl is considerably more fat-soluble than desflurane and therefore has a less predictable half-life after prolonged administration.[23] This likely led to accumulation and prolonged emergence times, whereas the effects of desflurane wore off more rapidly due to its faster pharmacokinetics.[20,24–26] These results are shown in Figure 2. The changing track of desflurane–fentanyl effect-site concentration pairs was almost vertical during the wake-up process. In the 10–20-minute scale, the fentanyl effect-site concentrations decreased little compared with

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those of desflurane. The initial fentanyl effect-site concentration had a greater effect on the total wake-up time.

We attempted to determine which of the three different initial fentanyl effect-site concentration groups had a shorter wake-up duration with a low risk of poor analgesia quality. Wake-up durations were longer for patients in Group H ($>$ 2 ng/mL) than those in Group I ($\geq$ 1 ng/mL, $<$ 2 ng/mL). Fentanyl was thus the limiting drug in defining the time to wake-up; the inhaled desflurane duration had little or even no influence. Using the model for no response to tibial pressure, Group L ($<$ 1 ng/mL) patients might have had a relatively high risk of inadequate analgesia. Maintaining steady-state effect-site fentanyl concentrations between 1 ng/mL and 2 ng/mL might be recommended for wake-up testing, as it provides the best balance of rapid arousal and adequate analgesia.

Remifentanil is an opioid with an ultra-short half-life and a super rapid clearance rate,[27] and it is currently recommended in the literature for wake-up testing during scoliosis surgery.[21,28] However, the drug itself may impair postoperative sleep.[2,28] Remifentanil is also a relatively expensive drug and it is not available in some parts of the world. Grottke and coworkers[21] concluded that an anesthetic regimen with desflurane and remifentanil facilitated more rapid emergence during spinal surgery, and permitted immediate neurological examination (a mean wake-up time of 6.2 ± 1.0 minutes). In our study, the intermediate fentanyl effect-site concentration (Group I) exhibited a mean wake up time of 7.9 ± 3.7 minutes, which was only 1–2 minutes slower than the desflurane–remifentanil group in Grottke et al's study.[21] However, Rehberg and colleagues[2] found that patients undergoing scoliosis surgery with intraoperative wake-up testing using remifentanil had impaired sleep quality that lasted up to 6-months post-operation. Our results suggest that the response surface model could help anesthesiologists administer a desflurane–fentanyl regimen that achieves a similar wake-up time to desflurane–remifentanil and avoids the potential long-term side effects of remifentanil.

In addition to the need for an adequate anesthetic regimen to permit immediate neurological examination, it is crucial to ensure intraoperative hemodynamic stability. Hypotensive anesthesia is widely used in spinal surgery to reduce blood loss and to facilitate attainment of a bloodless wound.[29] Nitroglycerin was infused in all patients in this study to ensure hemodynamic stability. This may be one reason for the high variability in initial fentanyl effect-site concentrations. However, it also provided an opportunity to identify the best anesthetic combinations for wake-up testing.

There are several limitations that may have affected our analysis. Firstly, there were only four and six patients in Groups L and I, respectively. These group sizes may be insufficient for statistical analyses given the observed patient-to-patient variability. A second limitation is that several studies have reported that the minimum alveolar concentration (MAC) and MAC-awake values over a range of patient ages.[30] Drug interactions such as reduction of MAC of desflurane with fentanyl[10,31] may also affect our results. The MAC for sevoflurane ranges from 1.58–2.05% in patients aged between 30 years and 50 years,[32–38] and for desflurane the range is 6.00–7.25%,[10,11,39–42] resulting in a sevoflurane/desflurane potency range of 1.3–1.8. MAC-awake ranges from 0.61–0.70% for sevoflurane,[36,38,43] and 2.42–2.60% for desflurane,[44,45] resulting in a potency range of 2.9–4.6. For the purposes of this analysis, we selected a potency ratio of 3.3, which overlapped the MAC and MAC-awake potency ranges. A different choice may have yielded different results. A third limitation is that the patient responses to pain were derived from the 30-PSI tibia pressure model, which may or may not fully represent intraoperative pain intensity. In the aforementioned volunteer study, OAA/S assessments, and the 30-PSI tibia pressure model were performed in the absence of ongoing pain and without an endotracheal tube in place. We used this model to predict the results of wake-up testing from general anesthesia in intubated patients with mild to moderate surgical pain. However, no volunteer study can fully emulate the complexities of the clinical environment. The differences between the volunteer study from which the models were based and the clinical environment in which the models were applied likely affected the predictive ability of the models to some degree. Furthermore, residual propofol and midazolam, which were given as an induction agent and premedication, respectively, may have had a minor influence on the study, although it seems likely that the concentrations would be too low to confound the model predictions.[5] Nitraglycerin, which was used in several patients to control blood pressure and minimize surgical site bleeding, may mask the pain response in patients.

In summary, rapid emergence and immediate neurological evaluation are highly desirable during wake-up tests. This clinical study provides evidence that desflurane–fentanyl-based anesthesia can achieve this goal. The steady-state effect-site concentration of fentanyl before the wake-up test of between 1 ng/mL and 2 ng/mL allowed an appropriate balance between rapid emergence and adequate analgesia. These encouraging results indicate that response surface models with simple relative potency relationships can be used for a variety of inhalation agent-opioid combinations.

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